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This Position Document addresses the risks and benefits of pesticide products containing the subject active ingredient. The Agency has determined that the use of products containing the subject active ingredient may meet or exceed a risk criterion described in 40 CFR Part 154. Potential hazards will be examined further to determine the nature and extent of the risk, and considering the benefits of the subject active ingredient, whether such risks cause unreasonable adverse effects on the environment.

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DECISION DOCUMENT

MERPHOS

Office of Pesticide and Toxic Substances

Office of Pesticide Programs

United States Environmental Protection Agency

Washington, D.C. 20460

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MERPHOS DECISION DOCUMENT

I. BACKGROUND

A. INTRODUCTION

This document presents the Agency's decision not to initiate the Rebuttable Presumption Against Registration (RPAR) review of merphos. This decision is based upon the conclusion that even though laboratory animal testing indicates suggestive evidence of neurotoxic effects, actual field use of the chemical has not demonstrated unreasonable adverse effects to man or the environment. If the chemical were a neurotoxin of concern, the Agency would expect to see adverse effects in the field since neurotoxic effects are readily detectable within the approximate timeframe of chemical exposure. Moreover, the Agency has obtained agreements from registrants for label changes which specify protective clothing for applicators to further reduce exposure. Based on the available animal data, the Agency has calculated margins for various groups of applicators who wear protective clothing and found that adequate margins of safety exist.

The Agency's review of this chemical and the rationale for its conclusions are presented as follows. Section I contains legal background and regulatory history, chemistry, product use, dietary exposure and applicator exposure information. Section II evaluates the available evidence on merphos and reaches conclusions about the toxicological effects of concern. Section III summarizes the conclusions and the regulatory actions which the Agency will take as a result of this review.

B. Legal Background and Regulatory History

The Federal Insecticide, Fungicide, and Rodenticide Act, FIFRA (7 U.S.C. Section 136 et seq.), as amended, gives the Environmental Protection Agency (EPA or the Agency) the authority to regulate pesticide products. In order to obtain a registration for a pesticide under FIFRA, a manufacturer must demonstrate that the pesticide satisfies the statutory standard for registration. That standard requires (among other things) that the pesticide perform its intended function without causing "unreasonable adverse effects on the environment" [FIFRA Section (3)(c)(5)]. The term "unreasonable adverse effects" is defined as "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide" [FIFRA, Section 2(bb)]. In effect, this standard requires a finding that the benefits of each use of the pesticide exceed the risks of use, when the pesticide is used in accordance with commonly recognized practices. The burden of proving that a pesticide satisfies the standard for registration is on the proponents of registration and continues as long as the registration remains in effect. Under Section 6 of FIFRA, the Administrator is required to deny or cancel the registration of a pesticide or modify the terms and conditions of registration whenever he determines that the pesticide does not satisfy the statutory standard for registration.

Merphos was referred to the Special Pesticide Review Division (SPRD) as a candidate for the Rebuttable Presumption Against Registration (RPAR) process primarily because published data indicate that the herbicide induced neurotoxic effects in laboratory animals.

During the time period this chemical has been in review, the 1978 amendments to the Federal Insecticide, Fungicide and Rodenticide Act were enacted. One major feature of these 1978 Amendments was Section (3)(c)(8), otherwise known as the Grassley-Allen amendment. Briefly, this amendment prohibits initiation of formal action (such as an RPAR review) to cancel, suspend or deny registration of a pesticide unless the action is based on a validated test or other significant evidence raising prudent concerns of unreasonable adverse risk to man or the environment. Defined, a "validated test" is one which is conducted and evaluated in a manner consistent with acceptable scientific procedure; "other significant evidence" is defined as that which relates to the uses of a pesticide and its adverse risk to man or the environment. It is intended that "other significant evidence" of adverse risks means factually significant information and is not to include evidence based on misuse of the pesticide, unless such use is generally recognized practice. In determining whether a particular pesticide raises "prudent concerns," the Agency examines the degree of toxicity of the pesticide, as well as the likelihood of human and environmental exposure. The Agency applies this approach to all its risk triggers, including oncogenicity and mutagenicity triggers which do not on their face take exposure into account. This approach allows the Agency to avoid the burdensome consequences of a RPAR procedure in those situations in which the uses of the pesticide at current levels of exposure do not appear to pose an unreasonable risk to man or the environment.

C. CHEMISTRY

The chemical name of merphos is tributyl phosphorotrithioite. Its molecular formula is $C_{12}H_{27}PS_3$. Its structure is as follows:

$$(CH_3-CH_2-CH_2-CH_2S)_3P$$

Merphos (tributyl phosphorotrithioite), a pale yellow, clear liquid has a molecular weight of 298.4. It boils at 115°C to 134°C at 0.08 mm Hg, and melts at less than 25°C . The specific gravity is 1.004 at 20°C.

Merphos is soluble in acetone, ethyl alcohol, benzene, hexane, kerosene, diesel oil, heavy aromatic naptha, xylene, and methylated naphthalene.

Merphos is oxidized by air to merphos oxide[1/] (Maddy, 1976) (S,S,S-tributyl phosphorotrithioate). Merphos oxide is registered and sold under the trade name of DEF, and, like merphos, DEF is an herbicide used as a cotton defoliant. Available data indiate that the oxidation reaction occurs rapidly in the field (within an hour) and therefore, residue data for merphos are measured as merphos oxide.

1/Concurrently with merphos, the herbicide DEF (the oxidation product of merphos) has also been subject to Agency review. Like merphos, DEF became a candidate for the Rebuttable Presumption Against Registration process primarily because published data indicated that DEF induced neurotoxic effects in laboratory animals. The conclusions drawn from the Agency's review of DEF are presented in a separate decision document.

D. Product Use

Nine registrants currently hold federal registrations for 11 products containing merphos, all of which are liquid formulations (6 pounds active ingredient per gallon) used for cotton defoliation prior to harvest; only two registrants, Rhone-Poulenc and Gowan Company, hold registrations of the technical products. As a cotton defoliant, merphos is applied at a rate ranging from 1.12 to 1.5 pounds active ingredient per acre. Aerial spray is the preferred mode of application (California, Texas, Arizona) except in the Mississippi Delta region, where — given the warm, humid climate — cotton plants grow taller than in other regions and where both ground and aerial applications are employed in order to reach cotton plants in their entirety.

E. Dietary Exposure

1. Tolerances

A tolerance for merphos has been established for only one commodity. On May 4, 1961, a tolerance for merphos in or on cottonseed was set at 0.25 ppm (40 CFR 180.186). Because merphos rapidly oxidizes to DEF in the environment, (Maddy, 1976) merphos applied as a cotton defoliant is likely to appear as residue in the form of DEF. Tolerances for DEF have been set for several commodities, as follows: cotton seed, 4 ppm; meat, fat, and meat by-products of cattle, goats, and sheep, 0.02 ppm (negligible residue); milk, 0.002 ppm (negligible residue) (40 CFR 180.272). There is no tolerance established for cottonseed oil because the residues in cottonseed oil are covered by the

residues in the raw commodity cotton seeds. The Food and Drug Administration also established a tolerance for DEF at 6 ppm for cottonseed hulls or for use as cattle feed (21 CFR 561.390).

2. Residue Monitoring

Very little data are available on the environmental fate of merphos. Because contact with air converts merphos to DEF (merphos oxide), data on the environmental fate of DEF serve to indicate the fate of merphos in the physical environment. In the absence of comparable data on merphos, much of the following discussion of environmental fate derives from data on DEF.

An investigation was conducted by Thomas and Harris (1965) with the dual purpose of 1) developing a gas chromatographic method for determining merphos as DEF in cottonseed and 2) applying this method in the analysis of cottonseed from cotton plants defoliated according to directions for use on the label for the products merphos and DEF. All treated samples received treatments of 2 pounds DEF active ingredient per acre. Samples were taken 1, 4, 8 and 11 days after treatment and analyzed by the colorimetric method as well as the gas chromatographic method. Both analytical methods showed that residues of DEF in or on cottonseed dissipate rapidly. Approximately 90 percent of DEF residues dissipated within 4 days (from 2.8 ppm net residue on day 1 of the preharvest interval to 0.35 ppm on day 4, using the colorimetric method; from 5 ppm net residue on day 1 to 0.6 ppm on day 4, using the gas chromatographic method).

To measure the dissipation of merphos and DEF residues in cotton fields, the California Department of Food and Agriculture conducted field studies in 1975, in which residues in or on cotton plants were measured at varying inter-

vals up to 9 days after application (Maddy, 1976). Five fields were studied, 2 of which were treated with merphos (Fields 2 and 4), and 3 with DEF (Fields 1, 3, and 5). Fields 1 through 4 were treated aerially, field 5 was treated via ground spray application. In Field 2 (near Bakersfield, Kern County), merphos was applied at a rate of 1.50 pounds active ingredient per acre (spray volume: 10 gallons/acre; tank mixture: 2 pints Folex, 1.5 pint Bolls'-Eye). One hour after application, residues of merphos were below detectable levels, while the average total residue of DEF (oxidized from merphos) in or on cotton foliage was 173 ppm; 5 days after application, average total residue was 11 ppm, likewise measured as DEF. In Field 4 (also near Bakersfield, Kern County), merphos was again applied at a rate of 1.5 pounds active ingredient (spray volume: 10 gallons/acre; tank mixture: 2 pints Folex, 0.5 pint paraquat, 0.12 pint K-90 spreader). One hour after application, the total residue of merphos in or on cotton foliage was 4.2 ppm, while the total residue of merphos oxide (DEF) was 147 ppm. Two days after application (samples stored 15 days at 8°C prior to extraction), residues of merphos were below detectable levels, while the average total residue of DEF was 64.2 ppm. The pattern of results shown in these field tests indicates that residues of merphos dissipate almost immediately and residues of DEF dissipate rapidly.

3. Dietary Exposure to the General Population

The Agency calculated worst case dietary exposure for a 16-year old male weighing 70 kg by assuming that the residues of merphos as DEF are at tolerance levels of (0.02 ppm) in the meat, (0.002 ppm) milk and oil and oil products from cotton seeds consumed in a 1.9 kg diet per day. While the Agency does not have data to indicate whether DEF is present at tolerance levels, the rapid dissipation of DEF would suggest that the tolerance assumption will overstate

dietary exposure.[2/] The calculation showed that the total maximum daily intake of DEF of 1.0×10^{-4} mg/kg b.w./day (Datta, 1978). A four kilogram infant ingesting 770 ml of milk per day would have a maximum total daily intake of DEF of 0.385×10^{-3} mg/kg/day. The residues of merphos itself would be expected to be zero.

F. Applicator Exposure (see Appendix A for detailed calculations)

1. Aerial Applicator Exposure

The EPA and the State of California monitored exposure potential to flagmen, mixer/loaders and pilots during application of merphos on cotton fields in the San Joaquin Valley (Peoples et al., 1981). Applicators wore protective clothing.[3/] Protective clothing including socks, shirt, pants and a washable cap, clean cotton long-sleeved and long legged coveralls, and rubber boots were required daily and were worn by mixer-loaders and flagmen.

2/ The Agency has data indiacting that DEF is not present even at the tolerance levels in milk, cottonseed oil, cottonseeds and cottonseed meal. The Food and Drug Administration (FDA) has monitored milk samples from 1972 through 1981, and found only trace amount of DEF (0.002 ppm) in one sample out of 5,000 samples tested. The FDA also monitors cottonseeds, cottonseed oil, and cottonseed meal for DEF residues which were found at levels much lower than the tolerance levels (cottonseeds, 0.06 ppm-trace; cottonseed oil, 0.55-0.37 ppm; and cottonseed meal, 0.14 ppm-trace).

3/ The principle manufacturer of merphos Rhone-Poulenc (who recently bought merphos registrations from Mobil Chemical Company) has agreed to the following label addition: For protection during field handling and field exposure, wear protective clothing such as rubber or neoprene gloves, long-sleeve shirts and knee-length boots to eliminate human contact, utilize closed system equipment, if available. Gowan Chemical Co. presently does not have any special protective clothing requirements on their merphos labels nor do the other end-use registrants.

Neoprene gloves were also worn by mixer-loaders and cotton gloves were worn by flagmen. Pilots wore shoes and socks, a helmet, clean long-sleeved shirts and long-legged cloth pants which were changed daily. All applicators worked a 7-hour work day.[4/] Merphos (Folex 6 lb. per gallon EC) was aerially applied by certified applicators at the rate of 1.12 to 1.5 pounds active ingredient in 5 to 10 gallons of water per acre. Closed systems for mixing and loading were used. [5/]

4/Seven hour work days are typical for professional certified aplicators. Virtually all aerial application is performed by professional certified applicators.

5/ Although the exposure estimates from this study include any benefits of closed systems due to the study design, Agency scientists believe that the protective clothing specified for mixer-loaders will achieve the same exposure reduction without the addition of closed systems. While closed systems can reduce exposure if they are working perfectly, current technology tends to result in cases where closed system mechanical failures can increase exposure.

a. Inhalation Exposure

The amount of merphos inhaled was measured by placing a Du Pont Constant Flow Sampler P-4000 pump on each worker. A total of 12 different breathing samples (4 for flaggers, 4 for pilots and 4 for mixer-loaders) were available for calculations. Each air sample tube was monitored for one to seven hours. the final results are summarized in Table 1.

Table 1. Concentration of Merphos as DEF Around Individual Workers During Aerial Application of Merphos[1/]

Types of Workers	Concentration of DEF ug/m^3 Air		
	No. of Workers	Average	Range
Pilot	3	7.6	4.8-9.0
Flagger	4	90.6	22.0-159.2
Mixer/Loader	4	61.2	10.6-80.8

1/ Based on a 7-hour period of measurement.

b. Dermal Exposure

The calculations for dermal exposures were based on the fact that the exposed workers wore long trousers, long-sleeved open-neck shirt and no gloves. The surface of face, back of neck, and the 'V' of the chest were considered the exposed area. These facts were taken into account to obtain an average case exposure estimate. Further, Peoples et al. (1981) measured merphos as DEF which fell on the patched area and the skin protected by cotton coveralls by attaching "patches" made of an outer layer of cloth and the inner layer of gauze taped together. Each subject was fitted with patches on the arms, legs, face and front and back of neck. Thus it was also assumed that 100% of the DEF measured from the bottom layer of the patches worn on the clothing would reach and be absorbed into the skin. Hand washes were made to determine exposure to the hands, this value was added to the amount calculated for the rest of the body.

The total average case dermal exposure values for the individual groups of workers are shown in Table 2.

Table 2. Calculated Daily Dermal Exposure Values for Individual Workers[1/] During Aerial Application of Merphos (Measured as DEF)

Types of Workers	Daily Dermal Exposure Values (mg/kg b.w./day)		
	No. of Workers	Average	Range
Pilot	4	0.08	0.05-0.11
Flagger	4	0.18	0.07-0.39
Mixer/Loader	4	0.32	0.16-0.54

1/ Assumes each individual works 7 hours continuously during aerial application of merphos and that the average male weighs 70 kg. It should be noted that merphos exposures (measured as DEF) are higher for mixer-loaders than the exposures measured as a result of DEF application at a similar application rate. The author noted that the firm applying merphos used a closed system that relies on operator force to puncture the container. This is considered to allow greater worker exposure due to the possibility of small spills. Also the rinse capabilities of these systems were not used by the firm applying merphos.

2. Exposure During Ground Application of Merphos

Since the Agency has no data available on merphos, DEF data has been used for both dermal and inhalation exposures. The Agency believes this is appropriate because DEF and merphos have similar chemical characteristics and would be expected to behave similarly in the field. Also, merphos oxidizes into DEF under field conditions. Although the protective clothing labels for DEF and merphos are not identical at this time, the Agency is working with both sets of registrants to eliminate discrepancies.

Wilson et al. (1980) conducted a field exposure study with DEF using an applicator to estimate dermal and inhalational exposures. DEF was applied at the rate of 2.25 lbs. per acre in 25 gallons of water. This is the maximum application rate listed on the label.

The air concentration of DEF was measured at 0.014 mg/m^3. The estimated inhalation exposure is 0.00252 mg/kg/day assuming a breathing rate of 1.8 m^3/hr for a 70 kg applicator working 7 hours a day. Although some farmer ground applicators may work up to 10 hours a day, the exposure to complete the entire job each season would remain the same. Thus, the seven hour figure was used in the calculations.

Dermal exposure to DEF was measured by Wilson et al. (1980) by the analysis of patches worn on sleeves, shoulder, chest, thigh and legs of the applicator. An exposure of 117.5 mg which is equivalent to 1.68 mg/kg/day is calculated for a 70 kg ground rig operator working seven hours a day and wearing protective clothing (long trousers and open neck long-sleeved shirt but no gloves or hat).6/

Since this study was carried out on only one applicator, the usefulness of this study to determine a margin of safety is limited.

6/ Although the proposed label submitted by Rhone-Poulenc requires gloves but no hat for mixer-loaders, the current label when this study was performed did not require them. The Agency did not adjust for a hat or gloves since discussions are ongoing with the registrants on this subject. It may be difficult to wear gloves while driving a rig and if the rig has a canopy, a hat may be unnecessary.

II. MERPHOS AS A POTENTIAL RPAR CANDIDATE

Merphos was referred to the EPA as an active ingredient suspected of meeting the 40 CFR 162.11 risk criteria warranting a rebuttable presumption. Delayed neurotoxicity as a potential hazard of the pesticide was the basis of concern.

40 CFR 162.11(a)(3)(ii)(B) provides that "a rebuttable presumption shall arise if a pesticide's ingredient(s), metabolite(s), or degradation product(s) ... produces any ... chronic or delayed toxic effect [including neurotoxicity] in test animals at any dosage up to a level, as determined by the Administrator, which is substantially higher than that to which humans can reasonably be anticipated to be exposed, taking into account an ample margin of safety."[1/]

To determine whether merphos poses a neurotoxic risk warranting a rebuttable presumption, the Agency has reviewed and evaluated all currently available data.

1/ Certain organophosphate compounds cause a specific type of irreversible neurotoxicity commonly referred to as organophosphate induced delayed neurotoxicity. In this syndrome irreversible damage to motor nerves appears approximately two weeks after a single effective dose of the organophosphate. At this time the acute toxic effects of the compound have disappeared. The effect can also be produced by small daily doses of the compound which have no apparent immediate toxic effect. Histologically the condition is characterized by a degeneration of motor axons, particularly those serving the legs, followed by myelin degeneration. For reasons that are unknown at present, this toxicity cannot be demonstrated in the common experimental animals (rat, mouse, dog, etc.) and is best demonstrated in the adult chicken.

A. Animal Tests (see Appendix B for detailed list of studies)

Indications that merphos might induce neurotoxic effects were first reported by Casida et al. (1963). In an experiment performed with two groups of White Leghorn hens, merphos was administered intraperitoneally in corn oil at daily doses of 100 mg/kg. One group was treated for 10 days and the second group for 7 days. Ataxia was reported in the first group on day 25. In the second group, ataxia was observed on day 33. The exact number of hens used in this experiment or the percentage exhibiting ataxia was not indicated, nor was a histopathological examination reported.

In 1964, Baron and Johnson reported on the neurological disruption produced in hens by merphos and DEF. Baron and Johnson (1964) reported that 4 of 12 White Leghorn hens given multiple intraperitoneal injections of merphos (100 mg/kg/day for 10 or 15 days) showed clinical signs of delayed neurotoxicity (peripheral weakness) as well as damage to the spinal cord. (A single hen was given intraperitoneal injections of 100 mg/kg merphos for only 5 days and showed no clinical signs and no damage to the spinal cord). Histopathological examination (using the Marchi stain) reportedly indicated that spinal cord disruption might have occurred before the onset of clinical ataxia. However, none of the 8 hens given oral doses of merphos up to 300 mg/kg for 10 days showed clinical signs of neurotoxicity, although histopathological examination reportedly revealed spinal cord disruption. These oral doses of merphos caused no mortality, and animals held for 50 or 60 days appeared normal at that time. This oral study (100 mg/kg and up to 300 mg/kg levels) in which positive histopathology accompanied by negative clinical signs results were observed, could not be repeated in experiments by Baron. He concluded that the original

observation of positive histopathology (while clinical signs were negative) was an artifact of the staining process. (Baron, personal communication with Zendzian, 1979).

In screening tests for the production of paralytic effect in White Leghorn or Rhode Island Red chicken hens, Gaines (1969) tested 9 carbamate and 30 organic phosphorous pesticides including merphos and DEF. All test chickens were given atropine sulfate in water solution by the oral route at a dosage of 15 mg/kg to protect them against the acute effect of each pesticide tested. Fifteen minutes later the pesticide was administered in peanut oil solution or suspension via subcutaneous injection under the wing. Test chickens were checked daily for signs of paralysis by placing them on the ground and observing their ability to walk. A single dose of merphos was then administered subcutaneously at 600 mg/kg to an unspecified number of hens. Hens (percentage unspecified) showed leg weakness beginning 3 to 21 days following injection with merphos and failed to recover completely by the end of the observation period of more than 30 days following injection.

A study designed to evaluate the potential neurotoxicity of merphos following a single topical application to White Leghorn hens was conducted by Cox and Babish (1977), and results were submitted to the Agency by Mobil Chemical Company. To establish the approximate dermal maximum tolerated dose (MTD) of merphos and tri-o-cresyl phosphate (TOCP), to be used as a positive control, Cox and Babish (1977) conducted a preliminary dose range-finding study in which the dermal maximum tolerated dose (MTD) for both chemicals was found to be

roughly 1.0 ml (approximately 1004 mg)/kg. For purposes of testing the neurotoxic potential of merphos, 60 hens over 9 months of age were randomly selected from stock. Ten hens were administered a single topical application of TOCP, 1 ml/kg (approximately 1160 mg/kg [calculated MTD]), as a positive control; 10 hens were treated with 1 ml/kg corn oil as a negative control. Forty test hens were treated topically with a single application of 1 ml/kg (approximately 1004 mg/kg [calculated MTD]) merphos. Topical applications were made to the closely clipped skin of the midscapular area. Positive signs of paralysis were observed in test hens and in positive control hens beginning 14 days after dosing with merphos and TOCP, respectively. While TOCP produced paralytic signs in 100% of positive control hens, and one death on the final day of the study, merphos produced paralytic signs in 25% of test animals (10 of 40 hens) and two deaths. In neither case did paralytic signs regress during the 21-day observation period. No neurotoxic signs were observed in hens treated with corn oil (negative controls). Upon histopathological examination, 6 of the 10 test hens which evidenced clinical signs of neurotoxicity reportedly showed signs of nerve damage ("six showed slight swelling of occasional to scattered fibers in the ventral funiculus, and at least three of those six showed amorphous material in several swollen fibers"). This microscopic evidence of neurotoxic effects in test hens was characterized as similar in type to that seen in positive controls treated with TOCP. No analogous changes were observed in negative controls treated with corn oil.

In contrast to the positive results reported by Cox and Babish (1977) following dermal application of merphos (neurotoxic effects in 10 of 40 test hens) negative results were reported by Babish and Cox (1977) when merphos was administered orally. This report was submitted to the Agency by Mobil Chemical

Company. For purposes of testing the neurotoxic potential of merphos by oral administration, 60 hens over 9 months of age were selected randomly from stock. As positive controls, 10 hens were given a single oral dose of TOCP, 500 mg/kg. As untreated controls, 10 hens were given corn oil in an amount equivalent to the oral dose of merphos administered to test hens (11 ml/kg).

Forty test hens were treated with a single oral dose of merphos, 11 ml/kg (approximately 10,450 mg/kg, which approximates the oral LD_{50} in White Leghorn hens as determined in pilot studies). Positive paralytic signs began to appear in TOCP-treated hens at the end of 2 weeks, as expected. Fifteen of the 40 hens treated with merphos died of the acute toxicity of the test chemical; no paralytic signs were observed. After 21 days, a second oral dose of merphos, 10,450 mg/kg, was administered to the 25 surviving test hens. This second administration of merphos was lethal to 11 hens; again no positive paralytic signs were observed during the second observation period of 21 days. Hens in the corn oil control group likewise exhibited no neurotoxic signs during either the first or second 21-day observation period.

The Agency contracted a study to be conducted by Dr. Abou-Donia of Duke University Medical Center to further investigate neurotoxic potential of merphos and to determine a no observed effect level (NOEL) (Abou-Donia, 1978; 1980). Abou-Donia conducted two separate experiments (1) single dose of merphos administered orally and (2) subchronic (90-day) oral administration of technical merphos at lower doses to adult laying hens of 19 months old weighing 1.3 to 2.4 kg. Abou-Donia used a grading system of T_1, T_2, T_3, T_4,

and paralysis in ascending order of toxicity to hens as follows: T_1, mild ataxia, as characterized by diminished leg movement, reluctance to walk, and a tendency to slide on the floor, or to fly; T_2, gross ataxia, characterized by disturbance in control of leg movement, with a change in gait; T_3, severe ataxia, a stage in which legs sprawl out in front, and the hen is unable to stretch or lower its legs; and T_4, ataxia with near paralysis, marked by difficulty in moving the legs, inability to walk, and a tendency to sit down on the hocks most of the time. Paralysis was described as the inability to use the legs to stand, at which stage chickens usually show difficulty in breathing and swallowing, and some birds show a rapid, irregular head tremor. Three hens each were used for administration of Tri-O-cresyl phosphate (TOCP) (500 mg/kg), parathion (30 mg/kg), atropine sulfate (300 mg/kg) and empty gelatin capsules to act as positive, negative, atropine sulfate and gelatin capsule controls, respectively.

For the acute study, three atropinized hens each were given single doses of merphos in gelatin capsules at doses of 100, 200, 300, 400, 500, 600, 700, 800, 900, 1,000 and 2,000 mg/kg body weight, observed for 90 days and then sacrificed. Histopathological examination was carried out on tissue samples of liver, brain, sciatic nerve and spinal cord which were negative for all doses. Clinical signs of ataxia were observed at the T_1 level for all the doses except 100 mg/kg a dose at which no ataxia were observed. By comparison, the positive control (TOCP) hens produced ataxia and paralysis, while parathion, atropine sulfate, gelatin capsules controls showed no signs of ataxia or other neurotoxic syndrome.

In Abou-Donia's subchronic (90-day) study, eight groups of 5 test birds were given oral daily doses in gelatin capsules of 0.5, 1.0, 2.5, 5.0, 10.0 or 20.0, 40.0 and 80.0 mg/kg for 90 days and then observed for additional 30 days and then sacrificed for histopathological examination (Abou-Donia, 1978; 1980). All the controls as described in single dose studies were also used in this study. Abou-Donia observed T_1, T_2 and T_3 levels of ataxia for all doses below 10.0 mg/kg doses except at the 0.5 mg/kg dose level. Only at 20 mg/kg and higher dose levels, was the T_4 level of ataxia or paralysis observed. T_3 levels of ataxia were observed at doses of 1.0 mg/kg to 5.0 mg/kg which regressed to T_2 and then to T_1 levels in all but one hen (Abou- Donia observed T_4 level of ataxia in one hen dosed at 1 mg/kg). At the 10.0 mg/kg dose, only the T_2 level of ataxia was observed which then regressed to T_1.

In an acute dermal study carried out by Abou Donia (Abou-Donia, 1980). Merphos was applied at 1,000 mg/kg (in acetone solution) to the comb of the hens and observed for 30 days. At the 1,000 mg/kg dose level, the T_4 level of ataxia and paralysis were observed and histopathological damage in the spinal cord was also observed. In a subchronic study 20 and 40 mg/kg daily doses of merphos (in acetone solution) were applied for 90 days on the comb of the hens and observed for an additional 30 days. At the 20 mg/kg dose the level, T_1 and T_2 levels of ataxia were found but histopathology was negative. At 40 mg/kg dose, the T_3 and T_4 levels of ataxia, and paralysis were observed, and histopathology was positive.

The work of Abou-Donia (1978) was audited by EPA-FDA audit team (Beneke and Zendzian 1980). The auditors concluded that although they found no serious problems with this study, the results cannot be used to determine a definitive

NOEL for delayed neurotoxicity. This conclusion was based primarily on the auditors opinions of Abou-Donia's scoring system. They reported:

"Dr. Abou-Donia's scoring system for signs of delayed neurotoxicity in the chicken utilizes five degrees of impairment labeled T_1, T_2, T_3, T_4 and paralysis in ascending order of severity. The observations are subjective, particularly in the T_1 and T_2 stages which are most important for determining a NOEL. Hens rated as T_3 or higher show abnormalities that can be readily demonstrated by placing the hen on the floor observing its actions. The T_2 stage may or may not be observable under the nonstandardized observing conditions utilized. Dr. Abou-Donia was unable to consistently demonstrate it in hens which he has rated T_2. The T_1 condition could be neither described by Dr. Abou-Donia nor demonstrated in hens which he had rated T_1" (Zendzian, 1980a).

Since merphos converts to DEF rapidly (usually within one hour of application) and since the agency has valid tests on the dermal and inhalation toxicity of DEF, it is felt that the toxicity of merphos can be approximated by using DEF data.

In 1978, Thyssen and Schilde performed a subacute dermal study on poultry (1978b). DEF was administered dermally to female adult chickens for three weeks, five days per week, for six hours per day. The dose levels were 0, 0.01, 0.03, 0.1, 0.3 and 1.0 ml/kg of body weight. Doses of 0.3 ml/kg and 1.0 ml/kg caused mortality of 50% and 100%, respectively. Obvious signs of delayed neurotoxicity were observed in the 0.1 and 0.3 ml/kg dose groups. The dose of

0.03 ml/kg (32 mg/kg) had no neurotoxic effects on the hens. The authors concluded that neurotoxic effects were seen only in the lethal dose range of 0.3 ml/kg (320 mg/kg) and at a dose 1/3 of the lethal dose range (i.e., 0.1 ml/kg). The Agency has accepted this study as valid.

Thyssen and Schilde (1978a) conducted another subacute inhalation study on chickens in which mature female chickens were exposed to DEF aerosol at concentrations of 8, 21 and 84 mg/m^3 for 6 hours per day, 5 days per week for three weeks. The only effects were observed at the highest dose — five of the ten animals died and the remaining five developed signs of delayed neurotoxicity. Histological indications of neurotoxicity were only seen in one of the five affected animals. The authors concluded that DEF produced a neurotoxic effect only in the lethal concentration range of subacute inhalation studies.

B. Epidemiological Evidence

For a 5-year period from 1968 to 1973, epidemiological data on 40 employees of Mobil Chemical Company, Charleston, South Carolina, were compiled under the supervision of the Pesticide Program at the Medical University of South Carolina (Keil, 1977). The results of this study were submitted to the Agency by Mobil Chemical Company. The 40 workers participating in the study represented approximately one third of Charleston plant employees involved in the manufacture and processing of pesticides and phosphorous chemicals, principally merphos. For purposes of the study, workers were divided into 5 groups of 8 individuals whose chemical exposure was similar in type and duration. In

particular, the 8 workers in "Group I" were subject to the greatest duration of exposure to merphos — 5,636 man days from the beginning of their employment to 1973, as compared to 411 man days in Group II and 25 man days in Group IV; groups III and V were exposed only to chemicals other than merphos.

The overall results of this epidemiological study do not indicate a connection between exposure to merphos and general adverse effects on the health of the workers involved. Because only one third of workers employed in 1968 agreed to participate, however, the scope of this particular study is admittedly limited, and Keil (1977) advised that its results probably cannot be generalized beyond the workers actually involved. Nevertheless, since some of these workers had relatively high exposures to merphos, and since neurotoxic effects are usually detectable to the individual without detailed medical tests and in a timeframe close to the exposure timeframe, the lack of noted neurotoxic effects is significant.

C. Accident Reports From Field Use

The Agency reviewed its files containing adverse reports on pesticides (EPA, 1981). These reports are obtained through the Pesticide Incident Monitoring System (PIMS). Most of these incidents come from California and none have come from the Mississippi delta region. Fifteen incidents involving merphos were reported over a period from 1966 to June 1981. There are two groups of reports contained in 15 incidents. One group contains 9 reports involving merphos alone and, in the 6 remaining incidents, the reports involved merphos with other ingredients. While the PIMS system is not 100% reporting,

it provides an excellent indicator of the severity of a field problem. Pesticides which result in serious acute effects show high numbers of PIMS reports. For example, the PIMS report on paraquat, a cotton defoliant showed 318 incidents over a 13 year period or approximately 24 per year. Also, PIMS reporting indicates reporting decreases after exposure reducing actions are taken (such as restricted use classification or addition of potective clothing requirements). Fifteen incidents over a 15 year period is a low incidence rate. Moreover, most of the reported effects were not severe. Persons accidently exposed to merphos developed acute effects of nausea, tightness of chest, blurred vision, and vomiting. Neurotoxic effects were observed in only one victim who was exposed to undiluted merphos. He was temporarily paralyzed but fully recovered in 14 weeks as discussed below.

A single case report is available on an individual who experienced neurotoxic symptoms following repeated, accidental dermal exposure while mixing undiluted merphos. Apparently, he had ignored label directions to wash contaminated clothing or skin and as a result of this misuse situation, exposure to excessive doses of undiluted merphos. According to a physician's report (Fisher, 1977), the man splashed his bare upper arms and T-shirt with what is described as a moderate amount of undiluted merphos. The T-shirt was reportedly soaked through to the skin, and the man did not wash off the substance or remove the shirt. During the next two days, he reportedly splashed smaller amounts of merphos on his bare arms.

Approximately 4 days after the initial incident, the subject noted weakness in his hands, arms and legs, and was diagnosed as having organophosphate poisoning. Later, the patient developed complete facial diplegia. After a period of hospitalization and physical therapy and care the patient recovered completely.

D. Conclusion

Positive neurotoxic responses have been reported in tests employing intraperitoneal administration (Casida et al., 1963: Baron and Johnson, 1964), subcutaneous injection (Gaines, 1969), dermal application (Cox and Babish, 1977) and oral administration (Abou-Donia, 1978; 1980). Negative results were reported by Babish and Cox (1977) for oral administration to hens. Although the positive studies provide qualitative evidence that merphos may have induced delayed neurotoxicity in chickens, none of these studies provide a basis for deriving a definitive no observed effect level (NOEL). Histological confirmation is lacking in many studies or is spotty, even in chickens that displayed neurotoxicity. None of the studies allowed sufficient post treatment time to determine whether or not the chickens could recover. Although recovery of the animals from merphos is not a key factor in deciding whether to initiate an RPAR review it would play an important role in the determination of the risk-benefit picture if existing margins of safety were not adequate.

The Agency has used the available data to calculate margins of safety. Studies appropriate to the route of administration are used to calculate NOELs but ranges are used where uncertainty surrounds the NOEL determination. Ranges

are also used in estimating applicator exposure. Because merphos degrades rapidly to DEF, DEF animal studies are used to estimate NOELs in cases where adequate merphos studies do not exist.

For the oral route, margins of safety (MOS) of 5,000-100,000 were calculated based on the assumption that a 70 kg adult male receives daily doses of merphos at tolerance levels (see Section I.E.3. above) and based on Abou-Donia's subchronic studies using 0.5 mg/kg/day or T_1 level (1.0 mg/kg/day) or T_2 level of ataxia (10.0 mg/kg/day) as NOEL's. MOS's of 1,300-26,000 were calculated for a 4 kg infant ingesting 770 gm of milk daily also based on Abou-Donia's study using 0.1 or 10.0 mg/kg/day. Abou-Donia's studies were used in this calculation because they were the most thoroughly conducted (90 days) oral studies which showed positive results. The NOEL ranges reflect the uncertainty in detecting clinical symptoms in the absence of positive histopathology.

For the inhalational route, MOS's were calculated for applicators exposed during aerial application (Peoples et al., 1981). Based on the average, exposure values for applicators and based on the inhalation NOEL of 21.0 mg/m^3 for DEF (Thyssen and Schilde, 1978a), the MOS's were in the range of 231-2763. The Thyssen study was used because its protocol most closely approximates the exposure scenario for professional applicators (e.g., 3 weeks of exposure per season).

MOS's for the dermal route were also based on the exposures measured for the applicators during aerial application (Peoples et al., 1981). Using the dermal NOEL of 32 mg/kg/day (Thyssen and Schilde, 1978b), MOS's for the average exposure levels were 100-400.

The Agency has calculated separate margins of safety for dermal and inhalation exposure since the animal studies reflect different NOELs. Normally, a single MOS would be developed. However, the exposure via inhalation is negligible when compared to the dermal exposure. (For ground applicators, Appendix A shows inhalation exposure is approximately 0.1% of dermal exposure. This same relationship would be true for aerial applicators). Therefore, the average range of the dermal margins of safety would accurately reflect the total margin of safety.

The acreage treated by ground applicators is 5 to 10 percent of the total acreage treated with DEF. The ground applications are carried out for the rank cotton in the Mississippi delta region by the owner or the farm hand and confined to the single farm of the average size of 150 acres (Datta, 1979). Since an applicator can defoliate 50 acres a day, he does not get dermal and inhalational exposures of DEF for more than three days during an entire growing season. As shown in Appendix A, the total exposure is 5.05 mg/kg/yr and the NOEL is 480/mg/kg/yr (Thyssen and Schilde, 1978b). The MOS is 95.

Most of the calculations of MOS's show significant safety margins. In addition, other significant factors are (1) whether neurotoxic effects have

been observed in exposed applicators and (2) whether current label use precautions are adequate, or should be modified to improve safety margins for applicators. The accident exposure reports show a low incidence of any effects and the low number of reported effects have been minor, reversible acute effects. It is reasonable to expect that the Agency would have been made aware of neurotoxic incidents had they occurred. First, neurotoxic effects such as paralysis occur a short time after initial exposure to merphos and are easily detectable. Second, EPA has a incident monitoring program; if neurotoxic effects caused by worker exposure to merphos occurred, such effects should have been recorded, only one such incident is known. California, a State where a great quantity of merphos is used, has a well respected incident monitoring program. No such incidents have been recorded by California and one is recorded by State of Arizona. In this case, an applicator spilled undiluted merphos on himself and suffered paralysis but fully recovered in 14 weeks. Such symptoms are not indicative of irreversible delayed neurotoxicity. Further, this incident represents misuse of the product, since the applicator did not change his clothing or wash his skin as required by the label. The Agency has reviewed an epidemiological study of workers exposed to merphos (Keil, 1977) which, although flawed, did not indicate a correlation between merphos exposure and adverse health effects. Based on these considerations, the Agency finds that there is no basis for prudent concerns of unreasonable adverse risk to man from dermal exposure.

One of the two registrants for merphos, Rhone-Poulenc Company, has recently submitted their modified product label to require protective clothing, including a long-sleeved shirt, long-legged trousers, shoes and socks. In addition, mixer-loaders should wear rubber or neoprene gloves. The other registrant, Gowan Company, has agreed to include above protective clothing language on their labels. The Agency believes these measures will recude applicator exposure so as to ensure that the MOS's used in the Agency calculations occur in real world application situations.

III. SUMMARY OF CONCLUSIONS AND REGULATORY ACTIONS

The conclusions and recommendations arising from this review of merphos as an RPAR candidate conclude that the existing studies indicate that merphos does not produce unreasonable risk to man or the environment. Animal laboratory studies on neurotoxicity indicate a possible hazard but field studies do not support the existence of a hazard. Moreover, if the Agency assumes protective clothing is used, adequate margins of safety, based on animal laboratory data, exist for the general population and for applicators. Thus, applying the RPAR criteria and Section 3(c)(8) of FIFRA, it is not appropriate to consider merphos as a candidate for RPAR and merphos will be returned to Registration Division. No additional data are needed at this time. EPA will continue to work with registrants to clarify protective clothing label requirements.

APPENDIX A

MARGINS

Exposure Site	Exposure Range	NOEL	Margins
Inhalation (Aerial)	0.091 - 0.0076 mg/m^3 of air	21.0 mg/m^3	$\frac{21}{0.091} = 231$
	(See Table 1)	(Thyssen and Schilde, 1978a)	$\frac{21}{0.0076} = 2763$ Margin 231 - 2763
Dermal (Aerial)	0.32 - 0.08 mg/kg/day	32 mg/kg b.w. day	$\frac{32}{0.32} = 100$
	(See Table 2)	(Thyssen and Schilde, 1978b)	$\frac{32}{0.08} = 400$ Margin 100 - 400
Ground Application	0.00252 mg/kg/day Inhalation Exposure	32.0 mg/kg/day	$\frac{480}{5.05} = 95$
		(Thyssen and Schilde, 1978b)	Margin is 95
Dermal	1.68 mg/kg/day Dermal Exposure	Total 15 applications (5 times a wk for 3 wks)	
Total	1.68 mg/kg/day Total Exposure for three days 1.68 x 3 = 5.05 mg/kg/yr	Total exposure for 3 wks 32 x 15 = 480 mg/kg/3 wks	
Dietary 70 kg (adult) 4 kg.(infant)	1×10^{-4} mg/kg/b.w. (Datta 1978) 0.385×10^{-3} mg/kg/b.w	0.5-10.0 mg/kg b.w./day (Abou-Donia 1979a)	$\frac{0.5 \text{ or } 10.0}{1 \times 10^{-4}} = 5000 - 100{,}000$ $\frac{0.5 \text{ or } 10.0}{0.385 \times 10^{-3}} = 1300 - 26{,}000$

APPENDIX B
SUMMARY OF NEUROTOXICITY STUDIES REVIEWED
MERPHOS

Report # or Author	Mode of Administration	Dose Levels and Doses mg/kg	Results
Abou-Donia (1978; 1980)	Oral	100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000 (single doses)	No clinical effects at 100 mg/kg. No histopathological damage at any dose level.
Ibid	Oral	0.5, 1.0, 2.5, 5.0, 10.0 20, 40.0, and 80.0 (every day for 90 days)	No clinical effects at 0.5 dose. Histopathological damage only at 80.0 mg/kg dose levels.
Gaines	Subcutaneous Injection	400 mg/kg 600 mg/kg	400 mg/kg is no effect dose level. Positive clinical effects at 600 mg/kg.
Baron and Johnson	Intraperitoneal	100 mg/kg for 10 days and 15 days	Positive ataxia. Positive damage in sciatic nerve and spinal cord.
Ibid	Oral	100, 150, 200 and 300 mg/kg for 10 days	No ataxia observed but damage in sciatic nerve and spinal cord.
Casida Baron, Eto and Engler	Intraperitoneal	100 mg/kg daily for 7 days and 100 mg/kg daily for 10 days.	Positive ataxia observed but histopathology is not reported.

APPENDIX B CONTINUED
SUMMARY OF NEUROTOXICITY STUDIES REVIEWED
MERPHOS

Report # or Author	Mode of Administration	Dose Levels and Doses mg/kg	Results
Babish and Cox	Oral	11 ml/kg(11044 mg) on day 1 and on day 22	No ataxia and no histopathological damage.
Cox and Babish	Dermal	1 ml/kg (1004 mg/kg)	Positive ataxia and leg weekness.
Abou-Donia (1980)	Dermal	1000 mg/kg single dose	Positive ataxia and positive histopathology.
ibid	Dermal	20 and 40 mg/kg daily for 90 days	T_1 and T_2 ataxia but negative histopathology at 20 mg/kg T_4 ataxia, paralysis and positive histopathology at 40 mg/kg.

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